PATENT SPECIFICATION (11) 1 487 457

1 487 457

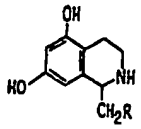
(21) Application No. 44807/75 (22) Filed 30 Oct. 1975
(31) Convention Application No. 49/134 734
(32) Filed 20 Nov. 1974 in
(33) Japan (JA)
(44) Complete Specification published 28 Sept. 1977
(51) INT CL² C07D 217/20; A61K 31/47//C07C 91/34, 119/06, 143/78; C07D 217/02, 217/06 (A61K 31/47, 31/05, 31/015, 31/085)
(52) Index at acceptance
C2C 1535 213 220 226 227 22Y 250 251 25Y 29X 29Y 305 30Y 322 326 328 32Y 351 355 364 365 366 368 36Y 385 43X 452 45Y 491 503 509 50Y 510 51X 534 620 62Y 633 634 638 644 650 652 658 662 672 676 67X 682 69Y 700 774 778 790 79Y BB LF MB MG SG WB WE

(19)

(54) 5,7-DIHYDROXY-TETRAISOQUINOLINE DERIVATIVES

(71) We, TANABE SEIYAKU CO. LTD., a company registered under the laws of Japan, of No. 21, Dosho-machi 3-chome, Higashi-ku, Osaka-shi, Osaka-fu, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel 5,7-dihydroxy-tetrahydroisoquinoline derivative and a process for preparing same. More particularly, it relates to compounds of the formula:



(I)

wherein R is trimethoxyphenyl, and pharmaceutically acceptable acid addition salts thereof.

It is known that 6,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline is useful as a bronchodilator (U.S. Patent 3,497,516). Said tetrahydroisoquinoline may be prepared by condensation of 6,7-dihydroxyphenethylamine with sodium 3-(3,4,5-trimethoxyphenyl)-glycidate or 3,4,5-trimethoxyphenylacetaldehyde. However, this condensation method can not be used for the synthesis of a tetrahydroisoquinoline having two hydroxy groups at the 5th and 7th-positions thereof because of the insufficient reactivity of 5,7-dihydroxyphenethylamine. The present invention provides a novel 5,7-dihydroxy-tetrahydroisoquinoline. It also provides a novel method of preparing a 5,7-dihydroxy-tetrahydroisoquinoline.

The 5,7-dihydroxy-tetrahydroisoquinoline derivative (I) of the present invention or a pharmaceutically acceptable acid addition salt thereof has potent bronchodilating activity and is useful as a bronchodilator. Moreover, as compared with 6,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline, the 5,7-dihydroxy-tetrahydroisoquinoline derivative (I) of the present invention is more useful because of longer duration of its potent bronchodilating activity and/or less side effects (e.g., less increase of heart rate). For example, when the bronchodilating activity of 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (hydrochloride) of the invention is estimated by the preventive effects against serotonin creatinin sulfate-induced bronchoconstriction after the duodenal administration thereof, said 5,7-dihydroxytetrahydroisoquinoline shows almost the same maximum preventive effects as that of 6,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (hydrochloride). Moreover, the bronchodilating activity of the former lasts for more than 3.5 hours at its maximum

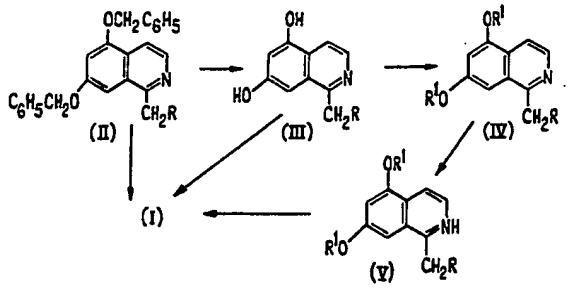
level, whereas the latter decreases to about ¼ times the maximum preventive effects after 3.5 hours of its duodenal administration.

The toxicity of the 5,7-dihydroxy-tetrahydroisoquinoline derivative (I) of the present invention is low. For example, the 50% lethal dose (LD_{50}) of 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (hydrochloride) which is estimated by intravenous injection thereof to mice is about 51 mg/kg.

The 5,7-dihydroxytetrahydroisoquiniline derivative (I) of the present invention can be used for pharmaceutical use either as the free base or a salt thereof. Pharmaceutically acceptable acid addition salts of the 5,7-dihydroxytetrahydroisoquinoline derivative (I) include, for example, hydrochloride, hydrobromide, perchlorate, nitrate, sulfate, phosphate, acetate, propionate, glycollate, lactate, ascorbate, maleate, fumarate, malonate, succinate, aspartate, glutamate and nicotinate. The 5,7-dihydroxytetrahydroisoquinoline derivative (I) may be used in the form of a pharmaceutical preparation for enteral or parenteral administration. The daily dose of the 5,7-dihydroxytetrahydroisoquinoline derivative (I) suitable for pharmaceutical use may be within the range of 10 to 500 μg/kg. Moreover, the 5,7-dihydroxytetrahydroisoquinoline derivative (I) may be used in conjunction or admixture with a pharmaceutical excipient which is suitable for enteral or parenteral administration. The excipient selected should be the one which does not react with the 5,7-dihydroxytetrahydroisoquinoline derivative (I). Suitable excipients include, for example, gelatin, lactose, glucose, sodium chloride, starch, magnesium stearate, talcum, vegetable oil and benzylalcohol. The pharmaceutical preparation may be a solid dosage form such as a tablet, a coated tablet, a pill, a troche, a capsule or pulveres; or in a liquid dosage form such as a solution, a suspension or an emulsion. The pharmaceutical preparation may further contain auxiliaries such as binders, diluents, stabilizing agents or emulsifying agents.

According to the present invention, the 5,7-dihydroxytetrahydroisoquinoline derivative (I) can be prepared by the steps of subjecting a 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (II) to partial catalytic hydrogenation to give a 5,7-dihydroxy-1-trimethoxybenzylisoquinoline (III), reacting said isoquinoline (III) with an organic acrylating agent, subjecting the resultant 5,7-diacyloxy-1-trimethoxybenzylisoquinoline (IV) to catalytic hydrogenation to give 5,7-diacyloxy-1-trimethoxybenzyl-1,2,3,4-tetrahydroisoquinoline (V), and then hydrolyzing the tetrahydroisoquinoline (V). Alternatively, the 5,7-dihydroxytetrahydroisoquinoline derivative (I) may be prepared by catalytic hydrogenation of the 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (II) or the 5,7-dihydroxy-1-trimethoxybenzylisoquinoline (III), (advantageously in the presence of platinum dioxide and preferably at a temperature of 5 to 40°C in a hydrogen atmosphere under one to 2 atmospheres pressure) and, if required, further converting the product into a pharmaceutically acceptable acid addition salt thereof.

The above-mentioned reactions of the present invention are shown by the following scheme:



wherein R^1 is an organic acyl group and R is the same as defined above.

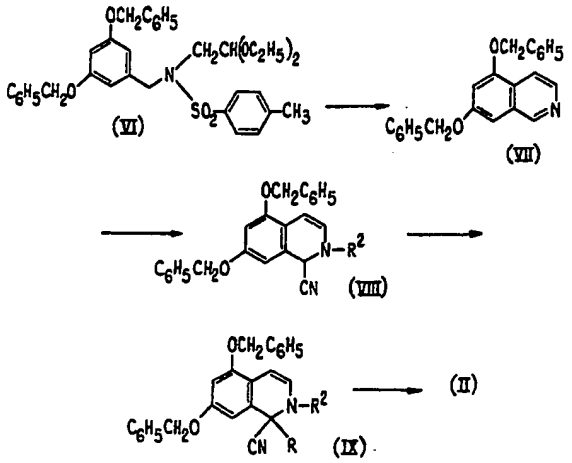
The partial catalytic hydrogenation of 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (II) can be conducted by shaking the isoquinoline (II) in the presence of a catalyst in a hydrogen atmosphere. It is preferred to carry out the reaction at a temperature of 5° to 40°C under atmospheric pressure. An alkanol (e.g., methanol, ethanol, propanol) or a mixture of an alkanol and water is suitable as the reaction solvent. Preferred examples of the catalyst include palladium, palladium-carbon, Raney-nickel and cobaltous dioxide. When platinum or platinum dioxide is employed as the catalyst in this hydrogenation reaction, a mixture of the 5,7-dihydroxytetrahydroisoquinoline derivative (I) and the 5,7-dihydroxy-1-trimethoxybenzylisoquinoline (III) may be obtained as the reaction product.

The subsequent reaction of the isoquinoline (III) with the organic acylating agent is accomplished in conventional manner. For example, said reaction can be carried out in the presence or absence of an acid acceptor. Suitable examples of the acid acceptor include organic tertiary amines (e.g., pyridine, triethylamine), alkali metal hydroxide (e.g., sodium hydroxide) and alkali metal carbonates (e.g., sodium carbonate). The reactive derivatives (e.g., acid halide, acid anhydride) of a fatty acid having one to 5 carbon atoms (e.g., acetic acid, propionic acid, butyric acid) and benzoic acid are suitably employed as the organic acylating agent. It is preferred to carry out the reaction at a temperature of 0° to 40°C. When pyridine is used as the acid acceptor, said reaction may be preferably carried out by dissolving the isoquinoline (III) to pyridine and then adding the organic acylating agent thereto under cooling. Further, when acetic anhydride is employed as the acylating agent, the 5,7-diacyloxy-1-trimethoxybenzylisoquinoline (IV) is prepared by heating said anhydride and the isoquinoline (III).

The catalytic hydrogenation of the 5,7-diacyloxy-1-trimethoxybenzylisoquinoline (IV) can be carried out in the presence of platinum or platinum dioxide in a hydrogen atmosphere. It is preferred to carry out the reaction at a temperature of 5° to 40° under one to two atmospheres pressure, especially under an acidic condition (e.g., pH 6 to 4). An alkanol (e.g., methanol, ethanol propanol) or a mixture of an alkanol and water is suitable as the reaction solvent.

The 5,7-dihydroxytetrahydroisoquinoline derivative (I) is prepared by acidic or alkaline hydrolysis of the resultant 5,7-diacyloxy-1-trimethoxybenzyl-1,2,3,4-tetrahydroisoquinoline (V). Said acidic or alkaline hydrolysis can be carried out by conventional manner, for example, by treating the isoquinoline (V) with a mineral acid (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide) or an alkali metal bicarbonate (e.g., sodium bicarbonate). It is preferred to carry out the hydrolysis at a temperature of 10° to 60°C in a solvent. Water, an alkanol (e.g., methanol, ethanol) or a mixture thereof is suitable as the reaction solvent. The 5,7-dihydroxytetrahydroisoquinoline derivative (I) is also prepared by catalytic hydrogenation of the 5,7-dihydroxy-1-trimethoxybenzylisoquinoline (III). Said catalytic hydrogenation may be conducted under same conditions as employed in the hydrogenation reaction of the 5,7-diacyloxy-1-trimethoxybenzylisoquinoline (IV).

The starting compound of the present invention, i.e., the 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (II), is a novel compound. This novel starting compound (II) is prepared by the steps of subjecting 1-[N-(3,5-dibenzyloxybenzyl)-N-*p*-tosyl-amino]-2,2-diethoxyethane (VI) to Pomeranz-Fritsch's intramolecular cyclization to give 5,7-dibenzyloxyisoquinoline (VII), reacting said 5,7-dibenzyloxyisoquinoline with an organic acylating agent and cyanogen hydride or an alkali metal salt thereof to give a 2-acyl-1-cyano-5,7-dibenzyloxy-1,2-dihydroisoquinoline (VIII), condensing an alkali metal salt of the dihydroisoquinoline (VIII) with a trimethoxybenzyl halide, and then hydrolyzing the resultant 2-acyl-1-cyano-5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (IX). These reactions are shown by the following scheme:



wherein R^2 is an organic acyl group and R is the same as defined above.

1-[N-(3,5-dibenzyloxybenzyl)-N-*p*-tosyl-amino]-2,2-diethoxyethane (VI) is readily obtainable. For example, said compound (VI) is prepared by condensing 3,5-dibenzyloxybenzaldehyde with 1-amino-2,2-diethoxyethane at 60° to 100°C, reducing the resultant 1-[N-(3,5-dibenzyloxybenzylidene)amino]-2,2-diethoxyethane with sodium borohydride in ethanol under refluxing to give 1-[N-(3,5-dibenzyloxybenzyl)amino]-2,2-diethoxyethane, and then reacting said product with *p*-tosyl chloride in pyridine under ice-cooling.

The Pomeranz-Fritsch's intramolecular cyclization is preferably conducted by treating the compound (VI) with an acid at a temperature of 80° to 110°C in a solvent (e.g., dioxane). Preferred examples of said acid include hydrochloric acid, sulfuric acid, phosphoric acid and p-toluenesulfonic acid.

The reaction of the 5,7-dibenzyloxyisoquinoline (VII) with the organic acylating agent and cyanogen hydride or an alkali metal salt thereof is carried out at a temperature of −5° to 20°C in a solvent (e.g., water, dichloromethane). The reactive derivative of an acid (e.g., benzoyl halide) is suitably employed as the acylating agent. When potassium cyanide is employed as the alkali metal salt of cyanogen hydride, this reaction is preferably carried out by dissolving the compound (VII) in methylene chloride, adding thereto an aqueous potassium cyanide solution, and then adding benzoyl chloride to the mixture at a temperature lower than 0°C.

The alkali metal salt of the dihydroisoquinoline (VIII) may be prepared by treating the dihydroisoquinoline (VII) with an alkali metal (e.g., lithium, sodium, potassium), an alkali metal hydride (e.g., sodium hydride, lithium hydride) or an alkali metal amide (e.g., sodium amide, potassium amide, lithium amide, lithium diisopropylamide, preferably under anhydrous conditions. The condensation reaction of a trimethoxybenzyl halide with the alkali metal salt of the dihydroisoquinoline (VIII) is carried out at a temperature lower than 0°C, especially lower than −10°C, in a solvent (e.g., dimethylformamide). The condensation product thus obtained, i.e., the 2-acyl-1-cyano-5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (IX), is then hydrolyzed to give the 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (II). Said hydrolysis can be readily carried out by treating the trimethoxybenzylisoquinoline (IX) with an alkali agent (e.g., alkali metal hydroxide, alkali metal carbonate) at a temperature of 30° to 80°C in a solvent (e.g., dioxane).

Practical and presently-preferred embodiments of the present invention are illustrated in the following Examples.

Example 1.

(1) 4.6 g of 3,5-dibenzyloxybenzaldehyde are added to 3.0 g of 1-amino-2,2-diethoxyethane, and the mixture is heated at 100°C for 10 minutes. Then, the mixture is stirred at 60°C for 2.5 hours under reduced pressure until water is removed from the mixture. 6.3 g of 1-[N-(3,5-dibenzyloxybenzylidene)amino]-2,2-diethoxyethane is thereby obtained as an oil. 5.9 g of this product are dissolved in 100 ml of ethanol. 600 mg of sodium borohydride are added to the ethanol solution, and the mixture is refluxed for 2 hours. After the reaction, water is added to the mixture and the aqueous mixture is extracted with ethyl acetate. The extract is dried and then evaporated to remove solvent, whereby 5.0 g of 1-[N-(3,5-dibenzyloxybenzyl)amino]-2,2-diethoxyethane are obtained.

Infrared absorption spectrum:

$\nu_{max.}^{liquid}$: 3330, 1600, 1595, 1150,1060 cm^{-1}

12.7 g of 1-[N-(3,5-dibenzyloxybenzyl)amino]-2,2-diethoxyethane are dissolved in 60 ml of pyridine, and 5.6 g of p-tosyl chloride are added thereto under ice-cooling. The solution is allowed to stand at the same temperature for 4 hours. Then, the reaction solution is poured into ice-10% hydrochloric acid, and extracted with ethyl acetate. The extract is washed with water, dried and then evaporated to remove solvent. 12.6 g of 1-[N-(3,5-dibenzyloxybenzyl)-N-p-tosyl-amino]-2,2-diethoxyethane are thereby obtained as an oil.

Mass analysis: m/e 589 (M^+).

(2) 8 ml of 10% hydrochloric acid are added to 46 ml of a dioxane solution containing 12.6 g of 1-[N-(3,5-dibenzyloxybenzyl)-N-p-tosyl-amino]-2,2-diethoxyethane. The mixture is stirred at 90°C for 24 hours. Then, the mixture is poured into ice-water. The aqueous mixture is alkalified with potassium carbonate and extracted with ethyl acetate. The extract is washed with water, dried and then evaporated to remove solvent. The crude product thus obtained is recrystallized

from ethanol. 3.3 g of 5.7-dibenzyloxyisoquinoline are thereby obtained as colorless crystals. Yield: 48.5%. M.p. 113—115°C.

(3) A solution of 3 g of potassium cyanide in 15 ml of water is added to 25 ml of a methylene chloride solution containing 3.3 g of 5,7-dibenzyloxyisoquinoline. 6.4 g of benzoyl chloride are added to the mixture at 0°C for 2 hours under stirring. After the mixture is allowed to stand at room temperature, the methylene chloride layer is separated therefrom. The methylene chloride solution separated is washed with an aqueous 1% sodium hydroxide solution and water, respectively. The methylene chloride solution is then dried and evaporated to remove solvent. The oily residue thus obtained is dissolved in 10 ml of ether, and this solution is poured onto a silica gel column. The column is eluted with a mixture of ether and hexane. The eluate is evaporated to remove solvent, and the crystalline residue thus obtained is recrystallized from ethanol. 4 g of 2-benzoyl-1-cyano-5,7-dibenzyloxy-1,2-dihydroisoquinoline are thereby obtained. Yield: 64%. M.p. 123—125°C.

(4) Sodium hydride (prepared by washing 553 mg of 65% sodium hydride with absolute n-hexane) is suspended in 15 ml of dimethylformamide. A solution of 3.4 g of 2-benzoyl-1-cyano-5,7-dibenzyloxy-1,2-dihydroisoquinoline in 40 ml of dimethylformamide is added dropwise to the suspension at −10°C in nitrogen atmosphere. Then, a solution of 1.71 g of 3,4,5-trimethoxybenzyl chloride in 40 ml of dimethylformamide is added dropwise to the mixture for 30 minutes, and the mixture is allowed to stand at the same temperature for 30 minutes. The reaction mixture is poured into ice-water, and extracted with ethyl acetate. The extract is evaporated to remove solvent, whereby 2-benzoyl-1-cyano-5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-1,2-dihydroisoquinoline is obtained as a crude oil. The crude oil is dissolved in 200 ml of dioxane. 50 ml of an aqueous 10% sodium hydroxide solution are added to the dioxane solution, and this mixture is stirred at 50°C for 12 hours. After the reaction, the mixture is evaporated under reduced pressure to remove solvent. The residue thus obtained is extracted with methylene chloride. The methylene chloride extract is washed with water, dried and then evaporated to remove solvent. 3.1 g of 5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline are obtained as a crude product. Yield: 84%. M.p. 158—160°C (recrystallized from ethanol).

(5) 0.2 g of 5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline is dissolved in 250 ml of ethanol, and 0.05 g of 10% palladium-carbon is added thereto. The mixture is shaken at 25°C in hydrogen atmosphere. After the hydrogen uptake is completed, the catalyst is removed by filtration. The filtrate is evaporated to remove solvent. 0.125 g of 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline is thereby obtained as a crude product. Yield: 95%. M.p. 270—275°C (decomp.) (recrystallized from ethanol).

(6) 0.8 g of 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline is dissolved in 30 ml of pyridine, and 0.955 g of acetic anhydride is added thereto under cooling. The mixture is allowed to stand at room temperature for 4 hours. The reaction mixture is poured into water and extracted with ethyl acetate. The extract is washed with water, dried and then evaporated to remove solvent. 0.9 g of 5,7-diacetoxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline is thereby obtained as a crude product. Yield: 90.5%. M.p. 118—120°C (recrystallized from ethanol).

(7) 0.78 g of 5,7-diacetoxy-1-(3,4,5-trimethoxybenzyl)isoquinoline hydrochloride is dissolved in 200 ml of ethanol, and 0.3 g of platinum dioxide is added thereto. The mixture is shaken at 25°C in hydrogen atmosphere. After the hydrogen uptake is completed, the catalyst is removed by filtration. 50 ml of a hydrochloric acid-ethanol solution (the content of hydrochloric acid: 9%) are added to the filtrate, and this mixture is heated at 50°C for 5 minutes. Then, the mixture is evaporated to remove solvent, and the residue thus obtained is recrystallized from a mixture of ethanol and isopropyl ether. 0.6 g of 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride is thereby obtained. Yield: 94.6%. M.p. 240—243°C.

Example 2.

A mixture of 1.4 g of 5,7-dibenzyloxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline, 0.7 g of platinum dioxide, 100 ml of a hydrochloric acid-ethanol solution (the content of hydrochloric acid: 9%) and 50 ml of ethanol is shaken at 25°C in hydrogen atmosphere. After 150 ml of hydrogen is absorbed, the catalyst is removed by filtration. The filtrate is evaporated to remove solvent, whereby a mixture of 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-isoquinoline hydrochloride and 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline

hydrochloride is obtained. This mixture is recrystallized 3 times from ethanol, whereby 0.3 g of 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride is obtained. Yield: 40%. The physicochemical properties of this product are identical with those of the compound obtained in Example 1.

Experiments:

Bronchodilating activity:

Cats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.). Under artificial respiration (13—15 ml of air/kg/stroke, 30 strokes/minute) thereof, the cats were immobilized by intravenous injection of gallamine triethiodide (8 mg/kg). Serotonin-creatinin sulfate (=bronchoconstrictor) was injected intravenously to the cats at the dose of 20 μg/kg, and the intratracheal pressure was measured by means of a pressure transducer. Then, each one of test compounds was administered to the duodenum of the cats at the dose of 10 μg/kg, and the intratracheal pressure and the heart rate were measured with the passage of time. The bronchodilating activity was estimated by the preventive effects (%) of each test compounds against bronchoconstriction. The results are shown in the following Table.

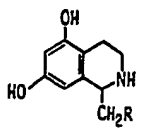
Period of time after the administration (minutes)	Preventive effects against bronchoconstriction (%)		Increase of heart rate (Number of heart beats increased/minute)	
	Compound A*	Compound B**	Compound A*	Compound B**
5	8.5±3.2	21.1±8.6	1.3±0.3	9.4±3.1
15	47.9±8.5	71.2±7.6	10.6±3.4	35.4±8.3
30	63.5±9.9	77.6±5.2	22.2±6.5	35.6±7.7
45	69.7±8.7	73.9±2.6	21.3±5.2	27.2±4.8
60	71.1±7.1	67.2±3.4	20.0±4.4	20.4±4.0
75	70.7±6.8	62.3±5.1	18.7±3.8	16.8±3.7
90	72.5±6.1	54.7±6.0	17.8±3.0	13.6±3.6
120	71.0±5.6	45.5±7.5	17.2±2.3	10.2±3.7
150	70.2±6.4	38.0±8.7	15.2±2.1	8.0±3.8
180	69.1±5.7	31.6±9.5	13.7±1.4	6.8±3.6
210	64.6±7.4	26.0±7.4	12.0±1.4	5.6±3.4

Note: *: 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (the compound of the present invention)

**: 6,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (the compound disclosed in U.S. Patent 3,497,516)

WHAT WE CLAIM IS:—

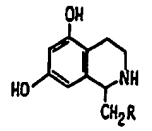
1. A compound of the formula



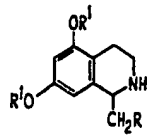
wherein R is trimethoxyphenyl, or a pharmaceutically acceptable acid addition salt thereof.

2. The compound of Claim 1, in which R is 3,4,5-trimethoxyphenyl.

3. A process for preparing a compound of the formula:



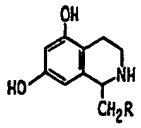
wherein R is trimethoxyphenyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises the step of hydrolyzing a compound of the formula:



wherein R^1 is an organic acyl group and R is the same as defined above, and if required, further converting the product into a pharmaceutically acceptable acid addition salt thereof.

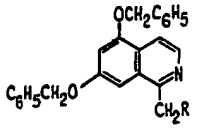
4. The process of Claim 3, in which said hydrolysis is carried out with a mineral acid, alkali metal hydroxide or alkali metal carbonate at a temperature of 10 to 60°C in a solvent.

5. A process for preparing a compound of the formula:



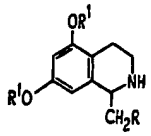
(I)

wherein R is trimethoxyphenyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises the steps of subjecting a 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline of the formula:



(II)

wherein R is the same as defined above, to partial catalytic hydrogenation to give the corresponding 5,7-dihydroxy-1-trimethoxybenzylisoquinoline (III), reacting said isoquinoline (III) with an organic acylating agent, subjecting the resultant 5,7-diacyloxy-1-trimethoxybenzylisoquinoline (IV) to catalytic hydrogenation to give a 5,7-diacyloxy-1-trimethoxybenzyl-1,2,3,4-tetra-hydroisoquinoline of the formula:



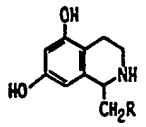
(V)

wherein R^1 is an organic acyl group and R is the same as defined above, hydrolyzing tetrahydroisoquinoline (V), and if required, further converting the product into a pharmaceutically acceptable acid addition salt thereof.

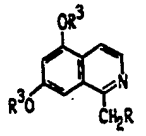
6. The process of Claim 5, in which the partial catalytic hydrogenation of the 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (II) is carried out in the presence of palladium, palladium-carbon, Raney-nickel or cobaltous dioxide at a temperature of 5 to 40°C in a hydrogen atmosphere, the reaction of the isoquinoline (III) with the organic acylating agent is carried out at a temperature of 0 to 40°C, the subsequent catalytic hydrogenation of the 5,7-diacyloxy-1-trimethoxybenzyl-isoquinoline (IV) is carried out in the presence of platinum or platinum dioxide at a temperature of 5 to 40°C in a hydrogen atmosphere under one to two atmospheres

pressure, and the hydrolysis of the tetrahydroisoquinoline (V) is carried out with a mineral acid, alkali metal hydroxide or alkali metal carbonate at a temperature of 10 to 60°C.

7. A process for preparing a compound of the formula:



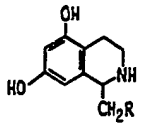
wherein R is trimethoxyphenyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises hydrogenating a compound of the formula:



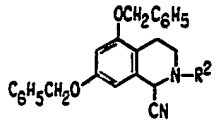
wherein R^3 is hydrogen or benzyl, in the presence of platinum or platinum dioxide, and if required, furthers converting the product into a pharmaceutically acceptable acid addition salt thereof.

8. The process of Claim 7, in which the catalytic hydrogenation is carried out at a temperature of 5 to 40°C in a hydrogen atmosphere under one to 2 atmospheres pressure.

9. A process for preparing a compound of the formula:

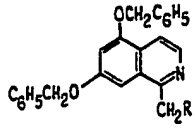


wherein R is trimethoxyphenyl, or a pharmaceutically acceptable acid addition salt thereof, which comprises the steps of condensing an alkali metal salt of a 2-acyl-1-cyano-5,7-dibenzyloxy-1,2-dihydroisoquinoline of the formula:



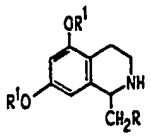
(VIII)

wherein R^2 is an organic acyl group and R is the same as defined above, with a trimethoxybenzyl halide, hydrolyzing the resultant 2-acyl-1-cyano-5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (IX) to give a 5,7-dibenzyloxy-1-trimethoxybenzyl isoquinoline of the formula:



(II)

wherein R is the same as defined above, subjecting the isoquinoline (II) to partial hydrogenation to give the corresponding 5,7-dihydroxy-1-trimethoxybenzylisoquinoline (III), reacting said isoquinoline (III) with an organic acylating agent, subjecting the resultant 5,7-diacyloxy-1-trimethoxybenzylisoquinoline (IV) to catalytic hydrogenation to give a 5,7-diacyloxy-1-trimethoxybenzyl-1,2,3,4-tetrahydroisoquinoline of the formula:



(V)

wherein R is the same as defined above and R^1 is an organic acyl group, hydrolyzing the tetrahydroisoquinoline (V), and if required, further, converting the product into a pharmaceutically acceptable acid addition salt thereof.

10. The process of Claim 9, in which the condensation of the alkali metal salt of the 2-acyl-1-cyano-5,7-dibenzyloxy-1,2-dihydroisoquinoline (VIII) with the trimethoxybenzyl halide is carried out at a temperature lower than 0°C, the subsequent hydrolysis of the isoquinoline (IX) is carried out with an alkali metal hydroxide or alkali metal carbonate at a temperature of 30 to 80°C, the partial catalytic hydrogenation of the 5,7-dibenzyloxy-1-trimethoxybenzylisoquinoline (II) is carried out in the presence of palladium, palladium-carbon, Raney-nickel or cobaltous dioxide at a temperature of 5 to 40°C in a hydrogen atmosphere, the reaction of the isoquinoline (III) with the organic acylating agent is carried out at a temperature of 0 to 40°C, the subsequent catalytic hydrogenation of the 5,7-diacyloxy-1-trimethoxybenzylisoquinoline (IV) is carried out in the presence of platinum or platinum dioxide at a temperature of 5 to 40°C in a hydrogen atmosphere under one to two atmospheric pressure, and the hydrolysis of the tetrahydroisoquinoline (V) is carried out by treatment with a mineral acid, alkali metal hydroxide or alkali metal carbonate at a temperature of 10 to 60°C.

11. A process for the preparation of a compound of the formula given in Claim 1, substantially as hereinbefore described and illustrated by the foregoing Examples.

12. A compound of the formula given in Claim 1 when prepared by a process in accordance with any one of Claims 3 to 11.

13. A pharmaceutical composition which comprises a compound in accordance with Claim 1, Claim 2 or Claim 12 and a pharmaceutically acceptable carrier therefor.

ALAN TROMANS & CO.,
Chartered Patent Agents,
7 Seymour Road,
Finchley,
London, N3 2NG.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.